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The effects of COVID-19 on placental morphology

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ABSTRACT

The impact of the COVID-19 infection, caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), during the pandemic has been considerably more severe in pregnant women than non-pregnant women. Therefore, a review detailing the morphological alterations and physiological changes associated with COVID-19 during pregnancy and the effect that these changes have on the feto-placental unit is of high priority. This knowledge is crucial for these mothers, their babies and clinicians to ensure a healthy life post-pandemic. Hence, we review the placental morphological changes due to COVID-19 to enhance the general understanding of how pregnant mothers, their placentas and unborn children may have been affected by this pandemic. Based on current literature, we deduced that COVID-19 pregnancies were oxygen deficient, which could further result in other pregnancy-related complications like preeclampsia and IUGR. Therefore, we present an up-to-date review of the COVID-19 pathophysiological implications on the placenta, covering the function of the placenta in COVID-19, the effects of this virus on the placenta, its functions and its link to other gestational complications. Furthermore, we highlight the possible effects of COVID-19 therapeutic interventions on pregnant mothers and their unborn children. Based on the literature, we strongly suggest that consistent surveillance for the mothers and infants from COVID-19 pregnancies be prioritised in the future. Though the pandemic is now in the past, its effects are long-term, necessitating the monitoring of clinical manifestations in the near future.

1. Introduction

The novel corona virus, SARS-CoV-2, discovered in Wuhan, China (2019), led to the calamitous pandemic, which left a massive death toll at its peak, resulting in several health-related repercussions which impacted healthcare, including maternal and foetal outcomes [1]. The virus, with an incubation period of ~5 days (range, 2–14 days), results in symptoms including headaches, fever, diarrhoea, myalgia, cough, severe respiratory illness and death depending on its severity [1]. Notably, pregnant women and their unborn children are considered high-risk populations, as pregnancy-related infections correlate with a greater risk of morbidity and death [2,3]. In 2020, a total of 3,613,647 births were recorded in the United States, with 225,225 women delivering during the pandemic and approximately 6.9% of these births being affected by COVID-19 [4,5]. This was alarming for the healthcare system, as the effects of COVID-19 on pregnancies are still to be fully determined [6].

Mechanical and physiological alterations during normal pregnancies

can significantly affect the immune system, respiratory system, susceptibility to infections, cardiovascular function and coagulation [2,7]. In addition, studies in pregnant women have shown that COVID-19 can result in haematological changes, inflammation that can or may result in a 'cytokine storm' and hypoxia which have all been linked to high mortality [6–8]. Furthermore, once infection triggers the maternal immune response, this will impact on the development of the foetal immune and nervous system, which could potentially result in neural impairments of the unborn baby [9,10]. In addition, mothers who contracted COVID-19 have been found to have a greater risk of preterm labour and pre-eclampsia [11]. On the other hand, there have been reports of the placental unit and foetus being unaffected by COVID-19 [12,13]. Hence, further research is needed on the placenta and its role in COVID-19 pregnancies since impairment to the placental function is central to a successful pregnancy.

A meta-analysis conducted by Wei et al. (2021) documented that the outcomes of a COVID-19 pregnancy, which can range from preterm birth, preeclampsia, chorioamnionitis, diabetes, lymphopenia, stillbirth,

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low birth weight and even neonatal death. Elsaddig and Khalil (2021) noted that pregnant women with COVID-19 are at a greater risk of adverse maternal outcomes, with many in their third trimester even requiring intensive care [14]. The exact factors underlying the link between COVID-19 and preeclampsia remains unclear. However, common pathways are expected, given their mutual impact on angiogenic pathways and vascular alterations [15]. Furthermore, foetal vascular malperfusion were documented in numerous pregnancies, which could possibly contribute to preterm birth, stillbirth and affect foetal growth [15,16].

The placenta has numerous critical functions, including protecting the foetus from infections, xenobiotic molecules and maternal diseases [17,18]. Its key role in a successful pregnancy necessitates an interrogation of the impact of infection especially given that the blood flow to this organ forms a substantive part of cardiac output [19]. The placental foetal unit plays a key role in protection through forming a selective barrier which prevents the movement of pathogens from the maternal to foetal circulation, with a mononuclear inner layer of cytotrophoblasts which play an essential role in autophagy and resistance for viral infections (Fig. 1) [16,20,21].

The design of the villi allows it to innately play a role in the defence within the placenta, with a syncytium that is selective to pathogen entry through different receptors which are able to recognize different pathogens [23–25].

Importantly, the surge in new-borns who were found to be COVID-19 positive has resulted in transplacental transmission becoming the focal point in COVID-19 transmission [26–29]. Furthermore, the possibility of antibodies from the mothers circulating blood passing through is of significance [30]. Indeed, a study conducted in the UK cohort reported that two of the five babies that died could have been due to COVID-19 complications, with one in 20 babies testing positive for COVID-19 in this study [12]. A case study conducted on 17 pregnant women in 2021, indicated that two neonates contracted COVID-19 and concluded that the SARS-CoV-2 infection could potentially result in preterm delivery and neonatal pneumonia [31]. Alarmingly, 25.5% of births were noted to be preterm in women who presented with COVID-19 [32]. Furthermore, a study conducted in Italy detected two cases of neonates who presented with COVID-19 as well as the SARS-CoV-2 genome in 2 placentas, 1 milk specimen, vaginal mucosa and the umbilical cord plasma indicating that mother-to-child transmission is possible [33]. Hence evidently COVID-19 can be transmitted through the placenta, thereby possibly affecting its structure and function [34,35].

Therefore, this review sheds light on the effects of COVID-19 in pregnancies, with its impact on the placenta being the focal point. It includes a background that covers the role of the placenta in COVID-19 pregnancies. Furthermore, the effects of COVID-19 on the placenta have been discussed, in addition to highlighting the link between COVID-19 and other gestational complications. Finally, the vaccine and therapeutic implications of COVID-19 on the placenta have been included in

this review together with recommendations for life post pandemic.

2. The effect of COVID-19 on pregnancies

The pathophysiology of COVID-19 in general has been extensively described [36]. The angiotensin converting enzyme 2 (ACE2) receptor (a component of the Renin-Angiotensin system-RAS) is the entry point for SARS-CoV-2 in the human body and has multiple implications in terms of physiological responses where RAS is the main protagonist [37,38]. Active replication of this virus results in, amongst other effects, an increase in inflammatory responses, and the dysregulation of the RAS including the downregulation of ACE2 which increases vascular permeability, inflammation and vasoconstriction [39]. Interestingly, Fenizia et al. (2020) postulated that modulation of ACE2 levels could possibly be associated with susceptibility to the SARS-CoV-2 infection in the placenta.

The SARS-CoV-2 virus is thought to be transmitted through the placenta by infecting the syncytiotrophoblasts of the villi resulting in an inflammatory response, or via the maternal blood through the uterine artery which will cross the interstitial space to enter the foetal circulation [40]. Furthermore, initially the virus infects the immune cells of the mother, thereafter transferring to the extravillous proximal trophoblast cells which allows it to be transmitted further to the core the villus and vasculature of the foetus [40].

Moreover, recent studies on COVID-19 pregnancies have noted several placental pathological changes, which include vascular and inflammatory alterations, placental infiltration, thrombo-embolic complications, necrosis and ischemia [7,41,42].

Various vascular pathological changes in placenta have been associated with the COVID-19 infection during pregnancy. These changes mainly include thrombosis, malperfusion and vasculopathy in both maternal and foetal circulations as summarized in Table 1. Vascular changes may adversely affect the health of pregnant women and their unborn babies and cause severe health consequences [43,44].

Placental vascular changes due to COVID-19 infections during the third trimester have been extensively studied. Studies documented signs of maternal vascular malperfusion which included the presence of infarcts, thrombosis, increased syncytial knots, increased fibrin deposition, villous agglutination and accelerated villous maturation [44, 47–54,56–60,62–65,68,71,73,74]. Furthermore, subsequent studies that reported multi case investigations of placentae from COVID-19 positive mothers which presented different features of foetal vascular malperfusion including avascular villi, karyorrhexis, mural fibrin deposition, villous hypoplasia and chorangiosis [44,46,48,49,51,54,56, 59,62,63,65,66,69,73]. Patberg et al. (2021) concluded that COVID-19 pregnancies exhibited an increase in histopathological abnormalities of the placenta, namely villitis of unknown aetiology and foetal vascular malperfusion. Infarction together with chorionic haemangioma in the placenta have also been documented in these past few years [61,75].

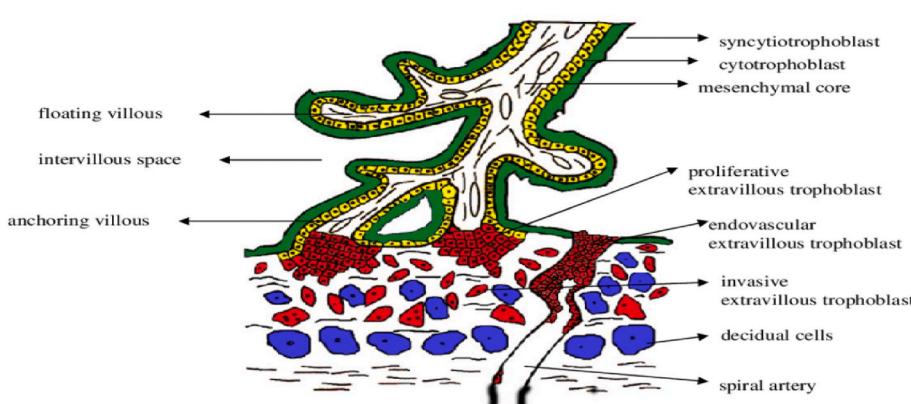


Fig. 1. Shows the schematic representation of the human chorionic villi highlighting the structure. The trophoblast differentiates into the extravillous trophoblast and villous. The villous is composed up of a monolayer of cytotrophoblastic cells from the floating villi (in the intervillous space) which are still attached the villous basement membrane. When these cells differentiate and proliferate, they form the external covering of the villus, the syncytiocytotrophoblast layer. Adapted from Evain-Brion and Malassiné [22].

Table 1

Vascular alterations reported in the placentas of COVID-19 pregnancies.

Placental pathological variations	Type of Study	Number of COVID-19 cases	Reference
- Decidual vasculopathy on the maternal surface	-Case Study	-1 Case	[45]
- Foetal vascular malperfusion.	-Case Study	-20 Cases	[46]
- Foetal vascular thrombosis			
- Avascular villi			
- Villous stromal-vascular karyorrhexis			
- Focal increase in perivillous fibrin deposition			
- Increased intervillous fibrin deposition	-Case study	-1 Case	[47]
- Maternal vessels thrombosis of capsularis decidua	-Case control study	- 15 COVID + Cases	[48]
- Intervillous hematoma		- 34 COVID - Cases	
- Maternal decidual vasculopathy			
- Borderline massive perivillous fibrin deposition			
- Avascular and fibrotic villi and stroma-vascular karyorrhexis			
- Infarct			
- Chorionic plate infarct			
- Maternal vascular malperfusion	-Case study	-19 Cases	[49]
- Foetal vascular malperfusion			
- Intervillous thrombus			
- Decidual arteriopathy			
- Increased perivillous fibrin			
- Focal placental infarct	-Case study	-1 Case	[41]
- Possible elements of infarction	-Case study	-1 Case	[50]
- Increased perivillous fibrin deposition			
- Foetal vascular malperfusion	-Case study	-5 Cases	[51]
- Thrombosis in larger vessels			
- Villous stromal-vascular karyorrhexis			
- Avascular villi			
- Ischemic necrosis	-Case study	-1 Case	[52]
- Extensive intervillous fibrin depositions			
- Findings suggestive of ischemia	-Case study	-5 Cases	[53]
- Massive deposition of fibrin			
- Maternal vascular malperfusion.	-Case control study	-16 Cases	[54]
- Intervillous thrombi			
- Decidual arteriopathy			
- Villous agglutination			
- Central villous infarction			
- Peripheral villous infarction			
- Atherosclerosis and fibrinoid necrosis			
- Clustered avascular villi			
- Increased perivillous fibrin			
- Necrosis	-Case study	-1 Case	[55]
- Foetal vascular malperfusion	-Case control study	-51 COVID + Cases	[56]
- Maternal vascular malperfusion		-25 COVID - Cases	
- Subchorionic thrombi			
- Infarction	-Case study	-1 Case	[57]
- Peri-villous fibrin deposition			
- Maternal vascular malperfusion	-Case study	-8 Cases	[58]
- Increased syncytial knots			
- Increased focal perivillous fibrin depositions			
- Maternal vascular underperfusion	-Case study	-5 Cases	[59]
- Foetal vascular underperfusion			
- Intervillous thrombi			
- Avascular villi			
- Maternal vascular malperfusion	-Case study	-1 Case	[60]
- Subchorionic laminar necrosis			
- Multifocal infarction	-Case study	-19 Cases	[61]
- Different degree of fibrin deposition			
- Maternal vascular malperfusion	-Case control study	-27 COVID + Cases	[62]
- Fibrinoid necrosis			
- Retroplacental hematomas			

Table 1 (continued)

Placental pathological variations	Type of Study	Number of COVID-19 cases	Reference
- Increased perivillous fibrin deposition		-27 COVID - Cases	
- Foetal vascular malperfusion			
- Thrombosis of the foetal chorionic plate			
- Maternal vascular malperfusion	-Case study	-7 Cases	[63]
- Excessive villous infarction			
- Increased syncytial knots			
- Intervillous thrombosis			
- Increased fibrin deposition			
- Accelerated villous maturation			
- Foetal vascular malperfusion			
- Avascular villi			
- Maternal Vascular Malperfusion	-Case control study	-31 COVID + Cases	[64]
- Increased intervillous thrombus		-67 COVID - Cases	
- Increased syncytial knots			
- Decidual arteriopathy			
- Villous infarction			
- Increased intervillous fibrin			
- Maternal malperfusion	-Case study	-5 Cases	[65]
- foetal malperfusion			
- Foetal vascular malperfusion,	-Case control study	-77 COVID-19 + Cases	[66]
- Avascular villi		-56 COVID-19 - Cases	
- Mural fibrin deposition			
- Preplacental hypoxia	-Case control study	-23 COVID + Cases	[67]
- Maternal vascular malperfusion	-Case study	-11 Cases	[68]
- Necrosis			
- Perivillous fibrin deposition	-Case study	-7 Cases	[69]
- Trophoblast necrosis			
- Foetal vascular malperfusion.			
- Maternal vascular malperfusion	-Case study	-50 Cases	[44]
- Extensive villous trophoblast necrosis			
- Foetal vascular malperfusion			
- Thrombohematomas	-Case study	-40 Cases	[70]
- Intervillous thrombus	-Case study	-1 Case	[71]
- Maternal arteriole with atherosclerosis			
- Extensive trophoblast necrosis			
- Perivillous fibrin deposition			
- Subchorionic and intervillous hemorrhages	-Case study	-1 Case	[72]
- Intervillous fibrin deposition			
- Massive perivillous fibrin deposition			
- Thrombi	-Case study	-4 Cases	[73]
- Necrosis			
- Perivillous fibrin deposition			
- Foetal malperfusion			
- Mural hypertrophy			
- Ectasis			
- Syncytial knots			
- Villous trophoblast necrosis	-Case study	-68 Cases	[74]
- Increased fibrin deposition			

Alterations in the uteroplacental circulation like malperfusion were attributed to hypoxia and shock [63]. Last year in South Africa Ramphal et al. (2022) documented vascular maladaptation, substantial fibrin deposition, an increase in villitis and vascular malperfusion. In addition to vascular alterations, pathological features indicative of inflammatory changes including chorioamnionitis/subchorionitis, intervillitis, chronic villitis and villous edema have also been identified in COVID-19 placentas as summarized in Table 2 [41,44,45,48–50,52–55,57–60,63,65,66,68–74].

Edlow et al. (2020) noted that a decrease in the expression of transmembrane serine protease 2 and angiotensin-converting enzyme 2 in the placenta can possibly protect the foetus against vertical transmission. However, aggregates of cytotoxic T lymphocytes as well as

Table 2

Shows alterations reported in the placentas of COVID-19 pregnancies which are indicative of inflammation.

Placental pathological variations	Type of Study	Number of cases	Reference
- Focal villous edema	- Case study	- 1 Case	[45]
- Histiocytic-neutrophilic intervillitis	- Case control study	- 15 COVID + Cases	[48]
- Chorionic vasculitis	- Case study	- 34 COVID - Cases	
- Villitis	- Case study	- 19 Cases	[49]
- Histiocytic intervillitis			
- Villous edema			
- Intervillitis	- Case study	- 1 Case	[41]
- Intervillitis	- Case study	- 1 Case	[50]
- Chronic intervillitis	- Case study	- 1 Case	[52]
- Mixed intervillitis/villitis	- Case study	- 5 Cases	[53]
- Chronic villitis	- Case control study	- 16 Cases	[54]
- Villous edema			
- Histiocytic intervillitis	- Case study	- 1 Case	[55]
- Villitis			
- Chronic intervillitis	- Case study	- 1 Case	[57]
- Mild acute intervillitis,	- Case study	- 8 Cases	[58]
- Edema			
- Chronic villitis	- Case Study	- 5 Cases	[59]
- Chorioamnionitis			
- Focal lympho-histiocytic inflammation (chronic villitis)	- Case study	- 1 Cases	[60]
- Chronic villitis	- Case study	- 7 Cases	[63]
- Chorioamnionitis/ subchorionitis			
- Lymphohistiocytic villitis	- Case study	- 5 Cases	[65]
- intervillitis			
- Villitis	- Case control study	- 77 COVID-19 + Cases	[66]
		- 56 COVID-19 - Cases	
- Chronic histiocytic intervillitis	- Case study	- 11 Cases	[68]
- Histiocytic intervillitis	- Case study	- 7 Cases	[69]
- Focal intervillitis	- Case study	- 50 Cases	[44]
- Placentitis	- Case study	- 40 Cases	[70]
- Intervillitis	- Case study	- 1 Case	[71]
- Chronic histiocytic intervillitis	- Case study	- 1 Case	[72]
- Villitis	- Case study	- 4 Cases	[73]
- Chronic histiocytic intervillitis	- Case study	- 68 Cases	[74]

histiocytes have been detected in the intervillous space and further confirmed through CD8, CD68 and CD3 immunohistochemical staining which support and suggest the detection of chronic intervillitis in COVID-19 placentas [52]. Chronic intervillitis as a result of COVID-19 has been reported to be indicative of the virus in the syncytiotrophoblast [76]. Furthermore, Schwartz et al. (2021) documented that the presence of both syncytiotrophoblast necrosis and chronic histiocytic intervillitis together can result in the increased risk for transplacental foetal infection. Transplacental transmission of COVID-19 was documented in a case where the neonate was born with neurological complications and upon further investigation perivillous fibrin deposition together with intervillitis and infarction were detected in the placenta [57]. Sadly, there have been stillbirth cases which have observed the combined presence of massive perivillous fibrin deposition, trophoblast necrosis and chronic histiocytic intervillitis in the placenta which have been identified as SARS-CoV-2 placentitis (Fig. 2) [69,74,77].

Placentitis results in destructive events within the placenta that can affect >75% of it, thereby impacting its function to provide oxygen to the foetus consequently causing malperfusion and neonatal death [77]. Increased subchorionic and intervillous fibrin in placentas attributed to maternal hypoxia, have been documented in a past study [78]. Also a case of intrauterine foetal death was recently attributed to coagulopathy and hypoxia as a result of placental dysfunction due SARS-CoV-2 placentitis [71]. Hence vascular changes together with inflammatory alterations caused by COVID-19 in the placenta can result in dire



Fig. 2. Shows sections of placental samples that have been affected by SARS-CoV-2. Image 1 shows serially sectioned placenta from a case showing appearance of SARS-CoV-2 placentitis. Microscopic examination showed massive perivillous fibrin deposition, chronic histiocytic intervillitis, and trophoblast necrosis. The extent of pathology resulting from these destructive lesions was greater than 90% and led to placental insufficiency and stillbirth. Image 2 shows gross pathological appearance of massive perivillous fibrin deposition that occurred with SARS-CoV-2 placentitis from a stillborn foetus. Intervillous thrombohematomas can be seen. Image 3 shows sectioned placental specimen from a case illustrating SARS-CoV-2 placentitis. There was 70% involvement of placental tissue with this destructive process [Adapted from Schwartz et al. (2022)].

consequences.

Furthermore, this virus often results in severe hypoxemia in pregnancy therefore altering the oxygen distribution to the placenta, as it is dependent on the uterine blood flow, fetoplacental system and maternal oxygen saturation [79]. Hypoxia and ischemia can be identified in the placenta through the increase in syncytial knots, whilst foetal hypoxia can be identified in the circulation through the increase in erythroblasts and nuclear debris [52,58,63,64,67,73]. Hypoxia induced by COVID-19 can result in altering the development of blood vessels, the blood supply as well as the development of the placenta which can have a devastating impact on the growing foetus [80]. This alteration in the blood supply and oxygenation due to COVID-19 is of critical interest, as in pregnancy, the demand for oxygen increases significantly, therefore with this

compounding effect, there is bound to be dysregulation in oxygen supply to the placenta [81,82]. This then leads to the assumption that these alterations in the blood supply to the placenta can be mechanistically responsible for the morphological changes observed in the past years. A previous study conducted on severe acute respiratory syndrome (SARS) observed similar morphological alterations in the placenta and deduced these may be as a result of the changes in the blood flow [78]. Furthermore, a study in rats documented reduced levels of oxygen in pregnancy, resulting in a surge of oxidative stress markers which are associated with malperfusion [83].

Alterations in the placental structure due to hypoxia were noted to be adaptive changes that occur in order to enhance placental function, however some changes may be suggestive of ineffective placental development and damage [84]. In addition to the morphological changes mentioned above in the placenta as a result of COVID-19, a study conducted last year found an abnormality in the umbilical cord of COVID-19 pregnancies to be high, whereby it attached to the margin of the placenta resulting in altered functioning and blood flow [82]. In addition, vascular remodelling in the arteries of the placenta in COVID-19 pregnancies have now been identified through histological examinations and documented [85]. Therefore, it can be speculated that in COVID-19 pregnancies the oxygen demand increases, however this demand is not met.

3. COVID-19 and other gestational complications

In the previous section, the hypoxic conditions experienced during COVID-19 pregnancies were highlighted. The presence of such conditions are known to put a pregnant individual under risk for other gestational complications such as preeclampsia and intrauterine growth restriction (IUGR) which can impact the development of the foetus [86,87]. This poses great concern as it leads to the question of whether COVID-19 and its effects have the ability to predispose and cause further gestational complications. This raises further concerns for women who are already diagnosed with gestational complications and then contract COVID-19.

Jamieson and Rasmussen (2021) documented that COVID-19 pregnancies are related to unfavourable consequences like premature births and preeclampsia [88]. Furthermore, in the USA, it was found that women with COVID-19 were 1.2 times more likely to develop preeclampsia [89]. SARS-CoV-2 was more likely to present in the placentas of preeclamptic women and could trigger hypertensive disorders in pregnant woman [90]. IUGR was also documented in a case where the foetus presented with this abnormality at approximately 36 weeks of gestation, following the mother contracting COVID-19 in the third trimester [91]. Furthermore, COVID-19 has been documented to be associated with increasing the risk of IUGR [92]. Villar et al. (2021) documented a link between elevated preeclampsia occurrence and COVID-19 however this association is yet to be confirmed, as COVID-19 and preeclampsia may result in similar pathological alterations [93].

Placental hypoxia has been noted to be a contributing factor in both preeclampsia and IUGR [86]. Interestingly we propose that the alterations observed in the placenta as a result of COVID-19, preeclampsia and IUGR are as a result of hypoxia.

Recent studies have found that changes seen in COVID-19 pregnancies mimic those that are seen in preeclampsia and preeclamptic women should therefore be considered high risk if they contract COVID-19 [94–96]. Hence we propose that COVID-19 alters the blood flow in pregnancy resulting in placental hypoxia which has been documented to result in preeclampsia and IUGR, and therefore COVID-19 can predispose one of these gestational complications with similar clinical manifestations [97,98].

4. COVID-19 vaccine implications in pregnancies

It is known that vaccines signify important public health-

advancement, through saving approximately 2–3 million lives yearly by providing adaptive immunity through generating antibodies upon exposure to a pathogen [99]. There are licensed vaccines available for 26 human pathogens and with the rapid rise in the number of vaccines becoming available, hesitancy towards vaccines have arisen with refusal differing across continents and cultures due to many concerns [100]. These concerns and hesitancy were further intensified with the implications of COVID-19 infections pertaining to maternal and foetal health [101]. In particular, vaccination during pregnancy protecting both the mother and unborn child from infection via the transfer of antibodies through the placental circulation (Immunoglobulin G- IgG) and mucosa (IgM, IgA, IgG) which releases antibodies into milk and colostrum to protect the neonate after birth [102]. However concerns around the COVID-19 vaccine only worsened with rumours of it eliciting antibodies that could attack the placenta thereby creating fear and anxiety in pregnant women, preventing them from considering the importance of this vaccine [103]. Furthermore, there has been a history of rumours about vaccines causing infertility which had also been circulated with the COVID-19 vaccine, where claims of cross reactivity between the human placental protein syncytin 1 and antibodies that recognize the SARS-CoV-2 spike protein emerged, resulting in many women declining this vaccine [103]. This despite the fact that, one should weigh the risk of a disease vs the risk of side effects of a vaccine when making a decision, as all types of medical treatment can pose adverse effects [99,100]. In keeping with this, the benefits of the COVID-19 vaccine outweighed the risks in pregnant women, as it posed minimal risk like side effects ranging from nausea to fever and myalgia [104]. Furthermore, studies have found that antibodies generated from the COVID-19 vaccine were able to be transferred through the placenta to foetuses providing passive immunity postpartum [105–107]. Thus far several studies have documented that the COVID-19 vaccines have elicited maternal responses as they were able to document the presence of maternal IgG as well as foetal IgM antibodies for SARS-CoV-2, as presented in Fig. 3 [105,106,108–110]. In addition, the presence of SARS-CoV-2 protein receptor binding domain (RBD) and spike (S) antibodies were detected in umbilical cords as well as infants [105,111]. Wang et al. (2021) observed that the IgG levels for the SARS-CoV-2 antibodies decreased drastically postpartum. Global data on the

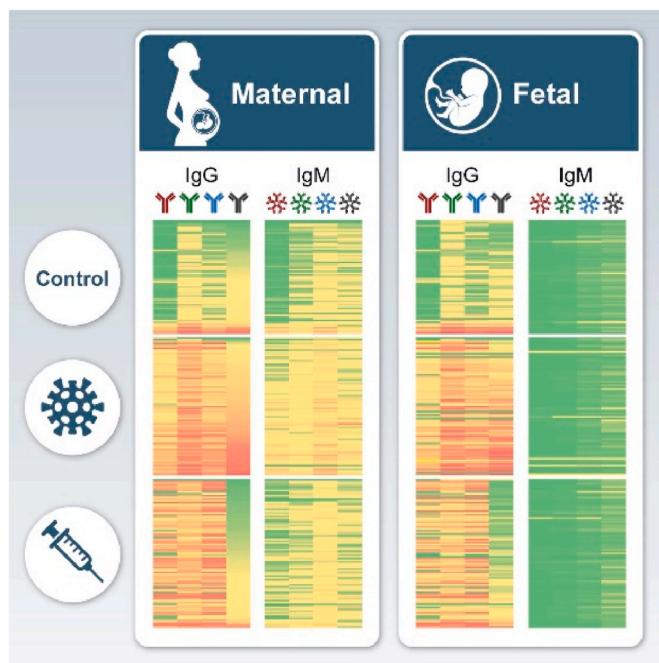


Fig. 3. A representative schematic diagram illustrated the maternal and foetal antibodies found after COVID-19 infection and vaccination [108].

uptake of the COVID-19 vaccine in pregnancies, infection rates and outcomes still need to be determined [112]. More importantly, the long-term effects of these vaccines still need to be established with critical focus on clinical manifestations that may arise due to these interventions.

5. Therapeutic implications

Therapeutic interventions during pregnancy, may pose threat to maternal and foetal health if not properly validated for safety. In this regard COVID-19 put an extra load by jeopardizing the ability to maintain a healthy pregnancy hence a host of new interventions were introduced [113,114].

Therapeutic interventions to treat COVID-19 included using various antiviral drugs, convalescent plasma (Passive immunotherapy) including using antiviral antibodies; nutritional supplements (folic acid, vitamin C, vitamin D); and miscellaneous treatments (Telbivudine, Azithromycin, Cobicistat) [114,115]. Significant efforts have been made to repurpose FDA-approved therapeutic drugs with known safety profiles during pregnancy in order to safely treat COVID-19 infection, which helped reduce the effects of COVID-19 therapeutic interventions [116]. However, some of the interventions mentioned above can have profound effects on pregnancy by affecting the placenta. Therefore, monitoring the impact of these drugs through investigating the physiological changes on the placenta would be beneficial in controlling future undesired side effects.

Pregnant women have been included in very few clinical trials for COVID-19 infection management (eg, SOLIDARITY trial [117], RECOVERY trial [117]). The severity of the mother's condition, underlying risk factors, gestational age, any potential maternal benefits, the likelihood of placental transfer, potential mechanisms for foetal harm, and the lack of knowledge regarding foetal and new-born risks should all be taken into account when deciding whether to use COVID-19-specific therapies during pregnancy. Patients being treated in hospitals may take the following medications presented in Table 3.

Several studies have observed pathophysiological changes in the placentas of COVID-19 positive patients [41,45,46,48,54,56,65,126]. Majority of these studies were able to report the pathological effects of COVID-19 but lacked a pharmacological and therapeutic perspective. However, a recent study was able to reveal that COVID-19 treatment with antivirals, antibiotics, low molecular weight heparins and chloroquine increased the weight and efficiency of the placenta compared to untreated group [127].

Further investigation into the effects of COVID-19 therapeutics and vaccines on the placenta and pregnancy in general are recommended to improve the health/safety of the mother and infant in the future.

6. Life after COVID-19

After exploring COVID-19 and the severity of its effects in pregnancy, it is critical to monitor the health of these mothers and new-borns to establish if there are any clinical manifestations as a result of the virus or its interventions. Many of the studies in this review reported no maternal deaths, illness or death in the new-borns as a result of COVID-19 [54, 58]. However there have also been reports of maternal death as a result of COVID-19 and new-borns presenting with infection after birth [128, 129]. Hence it is essential that these mothers and their new-borns from these COVID-19 pregnancies are monitored post-delivery and even after they recover as one is uncertain if the effects of COVID-19 will manifest clinically in the future. A study conducted by Liu et al. (2021) followed up with these infants for 9 months, where they observed transient early fine motor abnormalities in these babies born from COVID-19 pregnancies. However, we are still unaware of the long-term effects that COVID-19 and its therapeutic interventions may have, which will only manifest in the years to come, hence consistent surveillance on the mothers and new-borns from COVID-19 pregnancies need to be made a

Table 3
Therapeutic agents recommended for COVID-19 Pregnant patients.

Therapeutic agent	Indications	Dosing, Precautions and other considerations
Heparin	Venous thromboembolism prophylaxis in hospitalized patients.	<ul style="list-style-type: none"> - Prophylactic or intermediate dose (5000–10000 units twice daily (BID), subcutaneous (SC)) of unfractionated heparin for patients who might soon give birth [118]. - Prophylactic or intermediate dose (5000 or 40 mg OD, SC) of low molecular weight heparin for patients who are unlikely to be delivered within a few days [118].
Dexamethasone	<ul style="list-style-type: none"> - Patients who are on supplemental oxygen or ventilatory support. - Management of refractory shock in critically ill patients. 	<ul style="list-style-type: none"> - 6 mg orally or intravenously (IV) daily for 10 days After the initial four doses (6 mg, BID, IV) [119]. - Glucose monitoring and switching to other glucocorticoid should be considered as per WHO and the Society for Maternal-Foetal Medicine guidelines [120].
Nonsteroidal anti-inflammatory drugs (NSIAD) and Paracetamol	<ul style="list-style-type: none"> - When clinically indicated. - Low-dose aspirin for prevention of preeclampsia. 	<ul style="list-style-type: none"> - The lowest effective dose should be used. - Paracetamol is the drug of choice for antipyretic and analgesic effects [121].
Remdesivir	- Antiviral activity	<ul style="list-style-type: none"> - The potential for human placental transfer is unknown [121]. - No reported foetal toxicity during pregnancy [122].
Baricitinib, Tofacitinib	<ul style="list-style-type: none"> - Anti-inflammatory activity - Antiviral activity 	<ul style="list-style-type: none"> - The potential for human placental transfer is expected based on its molecular weight [123]. - Embryo-foetal toxicity have been observed in animal studies [123]. - Tofacitinib pregnancy outcomes were comparable to those in the general population.
Tocilizumab, Sarilumab, Siltuximab, Anakinra	- Anti-inflammatory activity	<ul style="list-style-type: none"> - Tocilizumab did not reveal clear serious safety signals during pregnancy [124]. - Less information is available about use of sarilumab, siltuximab, and anakinra in pregnancy [125].

priority. It is in the best interest of these mothers and infants to be screened for potential aftereffects.

7. Conclusion

This review has highlighted the impact that COVID-19 had on maternal and foetal health. The effects of COVID-19 observed in the placenta were concerning as it suggested that there were alterations in the blood flow which resulted in hypoxic conditions as the placenta and consequently the foetus were not receiving adequate blood supply. Furthermore, we found that this could result in predisposing mothers to

preeclampsia and IUGR resulting in further complications. Therefore, understanding the effects of the virus is imperative in determining therapeutic interventions to overcome current and even future adverse effects in both mother and baby. But most importantly, mothers and children from these pregnancies need to be monitored for any clinical manifestations that may arise in the years to come as a result of the alterations caused by COVID-19.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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